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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,998	06/14/2001	Maria Adele Pacciarini	01-270	1122
<div>7590 10/27/2010</div> <div>PETER I. BERNSTEIN BERNSTEIN, SCULLY, SCOTT, MURPHY & PRESSER 400 GARDEN CITY PLAZA GARDEN CITY, NY 11530</div>				
			EXAMINER KRISHNAN, GANAPATHY	
			ART UNIT 1623	PAPER NUMBER
			MAIL DATE 10/27/2010	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

09/786,998

Applicant(s)

PACCIARINI ET AL.

Examiner

Ganapathy Krishnan

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 August 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-23 and 25-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-23 and 25-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/02)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

The amendment filed 08/09/2010 has been received, entered and carefully considered.

The following information has been made of record in the instant amendment:

1. Claims 1-17 and 24 have been canceled.
2. Claim 25 has been amended. It has been made an independent claim.
3. Remarks drawn to rejections under 35 USC 112, second paragraph and 103.

The following has been overcome:

4. The rejection of Claim 25 under 35 U.S.C. 112, second paragraph has been overcome by amendment. Claim 25 as previously filed recited administration of MMDX is as a 5-10 minute bolus every eight weeks. Parent claim 18 recited infusion of from 15 to 30 minutes every four weeks. The time of administration and the frequency of administration were different from the range recited in the parent claim. Claim 25 has been amended as an independent claim.

Claims 18-23 and 25-37 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 18-23 and 25-37 under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (British Journal of Cancer, 1998, January, 77(1), 139-46, of record) in view of Horiguchi et al (Cancer Chemother. Pharmacol. 1992, 31 (Suppl I), S60-S64, of record) Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16, of record), Gorbunova (Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990, of record) and Brem et al (US 5,626,862, of record) is being maintained for reasons of record and is reiterated below.

Bakker et al teach that methoxymorpholino doxorubicin (MMDX, the active agent instantly claimed; Bakker uses the notation MMRDX instead of MMDX) is a drug that is active

against multi-drug resistant tumor cells (abstract; structural formula at bottom right of page 139). MMDX was administered to cancer patients via i.v. push (2-3 min) at a dose of $1.5\text{mg}/\text{m}^2$ for 4 weeks (part of the limitations of claims 18-19). Dose reduction was performed for grade IV neutropenia (page 141, left col. see under Treatment). As can be seen in Table 2 (page 140), the neutropenia observed in most of the patients is only in Grade I-II, which are at the low end of toxicity. According to Bakker the high tissue distributions and leukocyte levels of MMRDX (same as MMDX instantly claimed) is high and that it is still a very interesting compound in potentially more sensitive tumor types (page 145, left col. last four lines). Even though Bakker has not exemplified patients with liver cancer, the dosage levels as instantly claimed (instant claims 28-30 and 34-36) and the use of an agent like iodized oil (as in instant claims 26-27), his teaching shows that MMDX is still a good candidate for use in a method of treatment of other cancers like liver cancer. His teaching also shows that the dosage can be adjusted to reduce hematological toxicity levels and still maintain therapeutic levels.

Horiguchi et al teach that a formulation comprising lipiodol (the agent as recited in instant claims 26-27) and adriamycin showed a high tumor necrosis rate in five cases of hepatocarcinoma (the tumor recited in instant claim 21) after intra-arterial infusion (page S60 Abstract). Even though Horiguchi has used Adriamycin (Adriamycin is the trade name for doxorubicin: see page S60 right col. lines 7-8) as the active agent it can be seen from the structural formula (see page 139 of Bakker et al) that doxorubicin (adriamycin) has an NH_2 attached to the sugar ring whereas methoxymorpholino doxorubicin has the morpholino group at the same position. Since methoxymorpholino doxorubicin (MMDX) is structurally very close to adriamycin and is known to be active against tumor cell lines (according to Bakker et al) one of

ordinary skill in the art would use methoxymorpholino doxorubicin either alone or in combination with lipiodol for the treatment of liver cancer.

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). This means that methoxymorpholino doxorubicin can be used for the treatment of liver tumor/cancer (as it has broad spectrum antitumor activity) and can be administered by intravenous infusion as taught by Bakker.

Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract; limitations of claims 18-19 and 23). Based on the teaching of Gorbunova one of ordinary skill in the art will recognize that methoxymorpholino doxorubicin in combination with lipiodol (iodized oil) can be used for treating liver tumor/cancer via hepatic arterial infusion since it will create a high concentration of MMDX in the liver. If the cancer is in the liver that is where the MMDX is most needed.

Brem et al. teach delivery of chemotherapeutic agents for treating tumors in general. According to Brem et al. pulse or short term infusions of chemotherapeutic agents are better than continuous infusions (col. 1, lines 38-42). Adriamycin, which is closely related to MMDX has been suggested for administration for a period of at least a month (col. 7, line 65 and col. 8, lines 24-25). Even though this is with respect to Glioma this teaching of short term infusions and the time period can be applied to treatment of liver tumors and cancers. The time period for short

term infusion and frequency can be optimized for maximum beneficial effects and is well within the skill level of the artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising methoxymorpholino doxorubicin with iodized oil and use the same in a method of treating a human liver tumor/cancer and reducing systemic exposure as instantly claimed since such is seen to be taught in the prior art. It is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art in order to maximize the therapeutic effect and minimize side effects.

One of ordinary skill in the art would have been motivated to use MMDX in hepatic artery administration since prior art recognizes that hepatic artery administration of a chemotherapeutic agent is beneficial in treating tumor and reducing systemic exposure. Hepatic arterial administration also creates super high concentrations of the therapeutic agent in the organ affected and if the tumor/cancer is located in the liver such an administration is the logical choice. This localized administration is beneficial for reducing systemic exposure and reducing tumor volume in the liver. One would also make a composition comprising MMDX and lipiodol (iodized oil) since lipiodol in combination with Adriamycin has shown remarkable therapeutic effects for advanced cancer as taught by Horiguchi et al. Hence it is logical to make a composition comprising MMDX and lipiodol since MMDX is structurally close to Adriamycin and has broad spectrum antitumor activity. It is well within the skill level of the artisan to adjust dosages and frequency of administration since the prior art suggests reduction in dosage in order

to reduce side effects. The skilled artisan can adjust the dosage such that the beneficial effects are optimal and side effects are minimal.

Response to Applicants Arguments

Applicants have traversed the rejection of claims 18-23 and 25-37 under 35 USC 103 arguing that:

1. Bakker does not relate to liver cancer and to intra-hepatic administration. The patients in Bakker et al had head, lung, neck, colorectal and cervix cancer. The response rate was low using MMDX in renal and lung cancer. For head, neck and cervical cancer the effect of MMDX is unclear given low patient numbers. Bakker presents hedged results.

2. Horiguchi relates to adriamycin. Adriamycin is a very different drug than MMDX. MMDX is metabolized in the liver to a completely different metabolite using a completely different metabolic pathway than adriamycin. The biological effects of the two are exerted through different mechanisms. Horiguchi teaches that adriamycin is administered only with lipiodol. MMDX is contemplated by the instant invention, is effective in liver cancer even without its suspension in lipiodol. Its inclusion with lipiodol is merely a separate practice envisioned by the invention.

3. Kuhl examines the effect of MMDX on lymphoma and leukemia cells. It does not mention the treatment of liver cancer and hepatic artery injection.

4. Gorbunova reports toxicity of adriamycin up to level of Grade II-IV leucopenia for 50% of patients. This in no way renders obvious the Grade I leucopenia resulting with the

invention. Gorbunova would only lead one to employ increased dosages. In Gorbunova there was no objective response in a group of twelve patients in hepatic carcinoma using adriamycin.

5. Brem relates to pulse or short term administration and offers no meaningful input to the others.

Applicants' arguments have been considered but are not found to be persuasive.

1. Just because Bakker does not report results for liver cancer does not mean that it cannot be used for the treatment of the same or there won't be reasonable expectation of success. Bakker states (according to applicants) that response rate was low using MMDX in renal and lung cancer. For head, neck and cervical cancer the effect of MMDX is unclear given low patient numbers. Bakker's results and his statements that the response was low and unclear would not dissuade one of skill in the art from using it for the treatment of lung cancer. According to Bakker the high tissue distributions and leukocyte levels of MMRDX (same as MMDX instantly claimed) is high and that it is still a very interesting compound in potentially more sensitive tumor types. There is no teaching or indication that lung cancer will not be sensitive to the same treatment.

2. Horiguchi et al teach that a formulation comprising lipiodol (the agent as recited in instant claims 26-27) and adriamycin showed a high tumor necrosis rate in five cases of hepatocarcinoma (the tumor recited in instant claim 21) after intra-arterial infusion (page S60 Abstract). Even though Horiguchi has used Adriamycin (Adriamycin is the trade name for doxorubicin: see page S60 right col. lines 7-8) as the active agent it can be seen from the structural formula (see page 139 of Bakker et al) that doxorubicin (adriamycin) has an NH₂ attached to the sugar ring whereas methoxymorpholino doxorubicin has the morpholino group at

the same position. Since methoxymorpholino doxorubicin (MMDX) is structurally very close to adriamycin and is known to be active against tumor cell lines (according to Bakker et al) one of ordinary skill in the art would use methoxymorpholino doxorubicin either alone or in combination with lipiodol for the treatment of liver cancer. The structural features are not that much different that it would dissuade one of skill in the art not to use it. The mechanism by which MMDX and adriamycin exert their effect may be different. But from the teachings of Bakker and Kuhl it can be seen that MMDX is a potential candidate for the treatment of liver cancer irrespective of the mechanism of action.

3. Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). This means that methoxymorpholino doxorubicin can be used for the treatment of liver tumor/cancer (as it has broad spectrum antitumor activity) and can be administered by intravenous infusion as taught by Bakker. The fact that it is activated in the liver to a metabolite that is ten times more active will definitely persuade one of skill in the art to use it for treating lung cancer.

4. Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract; limitations of claims 18-19 and 23). Based on the teaching of Gorbunova one of ordinary skill in the art will recognize that methoxymorpholino doxorubicin in combination with lipiodol (iodized oil) can be used for treating liver tumor/cancer via hepatic arterial infusion since it will create a high concentration of MMDX in the liver. If the cancer is in the liver that is

where the MMDX is most needed. Gorbunova has used adriamycin. Kuhl also teaches that methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent.

5. Brem relates to pulse or short term administration. But his teaching would be used by one of skill in the art to use the same pulse and short term administration for the treatment of liver cancer using MMDX. It is meaningful from the point of view of administration of the active agent since Brem's teaching also relates to cancer treatment.

The instant invention is rendered obvious.

Conclusion

Claims 18-23 and 25-37 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623